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# Renal Function in Patients Treated with Cinacalcet for Persistent Hyperparathyroidism after Kidney Transplantation

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## Key Words

Cinacalcet • Kidney • Transplantation • Meta-analysis • Mimpara

## Abstract

**Background and Aim:** Cinacalcet effectively reduces calcium in patients with persistent hyperparathyroidism (HPT) after kidney transplantation. We aimed to assess the association of cinacalcet with a decrease in renal function based on a meta-analysis of observational studies in kidney transplant patients with persistent HPT. **Method:** Meta-analysis of observational studies, no randomized controlled studies were available. We calculated the mean difference between renal function before cinacalcet and at 3 months on cinacalcet treatment for each study. Pooled analyses are based on random effects models. **Results:** Pooling the studies on kidney transplant patients with persistent HPT (8 studies,  $n = 115$ ), we found a significant reduction in renal function ( $p = 0.008$ ). The effect size was  $5 \mu\text{mol/l}$  ( $p < 0.0001$ ) when pooling the 7 studies where serum creatinine levels were reported. Meta-regression analysis revealed that there was an association between renal function and the amount of calcium reduction under treatment with cinacalcet. A higher delta change in serum calcium levels was associated with a decrease in

renal function at 3 months of cinacalcet treatment. **Conclusion:** Cinacalcet treatment was associated with a decline of renal function in kidney transplant recipients with persistent HPT. Our meta-analysis underscores the need for frequent monitoring of creatinine and calcium levels during cinacalcet treatment.

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## Introduction

Cinacalcet is a calcimimetic drug that increases the sensitivity of the calcium-sensing receptor to extracellular calcium, which leads to a decrease of parathyroid hormone secretion and subsequently to lower serum calcium concentrations [1, 2]. The agent has been approved for treatment of dialysis patients with secondary hyperparathyroidism (HPT), and has substantially expanded the therapeutic options in the management of HPT.

Persistent HPT with subsequent hypercalcemia after renal transplantation occurs frequently [3, 4] and is a risk factor for bone disease, promotes vascular and tubulointerstitial calcifications and has been associated with decreased graft survival and enhanced post-transplant cardiovascular morbidity and mortality [5–8]. Effective con-

trol of persistent HPT is an important therapeutic goal after renal transplantation but poses a particular challenge. As active vitamin D treatment and calcium supplementation are contraindicated because they promote hypercalcemia, parathyroidectomy often remains the only therapeutic option. Encouraged by the success of cinacalcet to control biochemical parameters of HPT in dialysis patients [9], several studies including our own have shown that treatment with cinacalcet effectively corrects hypercalcemia in these patients [10–19]. Given the efficacy of cinacalcet to control hypercalcemia and the limited therapeutic options in these patients, cinacalcet has been off-label used in many transplant clinics. Hence, the awareness of a potential harmful effect of cinacalcet on renal function is of particular importance.

Yet, recently, investigators reported conflicting results of the effect of cinacalcet on renal function as well as cases of acute kidney failure after the initiation of cinacalcet in patients with intractable primary HPT [20]. However, the effect of cinacalcet on renal function was not investigated systematically. First, since cinacalcet treatment was established mainly in dialysis patients, a renal-specific adverse effect of cinacalcet would not have been detectable. Notably, renal function was not reported in phase III studies of patients with primary HPT [21]. Second, the planned phase III studies in kidney transplant patients with hypercalcemia due to persistent HPT are designed to test the profound effect cinacalcet has on parathyroid hormone (PTH) and serum calcium and thus smaller effects on renal function will perhaps not be found.

The primary goal of our analyses was to determine the short-term effect of cinacalcet on renal function in renal transplant patients with persistent HPT by performing a systematic review of the literature and a meta-analysis of peer-reviewed reports.

## Methods

### *Search Strategy and Data Extraction*

We conducted a systematic search for relevant English and non-English publications using Medline (Ovid, Pubmed) for the period January 1990 to August 2009 and EMBASE for January 1990 to August 2009. We searched reference lists and abstracts presented at the American Society of Nephrology from 2002 to 2008. Search terms included 'cinacalcet' or 'mimpara' or 'sensipar' or 'calcimimetic\*' or 'R586'. Eligibility and exclusion criteria were pre-specified. No consensus procedure was necessary because identical data were extracted by the two reviewers (J.H., A.L.S.). Eligibility and exclusion criteria as well as subgroup variables for potential sources of heterogeneity and their priority were pre-specified.

### *Eligible Studies*

We included trials that studied oral cinacalcet in adult kidney transplant patients with the diagnosis of HPT with a minimum follow-up of at least 1 month. To be included in the primary analysis, we required that renal function was assessed at baseline and at follow-up (>1 month and  $\leq 3$  months). Eligible studies that did not meet the criteria for the primary analysis were included in a sensitivity analysis including studies with different follow-up times among study participants.

### *Ineligible Studies*

We excluded case reports, reviews, letters, editorials, and non-peer-reviewed publications. We also excluded animal investigations, phase I studies, studies in patients on dialysis, studies on patients with primary or secondary HPT, studies on lithium-induced HPT and studies on patients with hyperparathyroid carcinoma.

### *Definitions*

Our primary outcome measure was the mean difference of renal function between baseline and follow-up for each study assessed by pre-/post-treatment serum creatinine or estimated or measured GFR.

### *Studies Identified for Primary Analysis*

A total of 8 separate studies were identified in patients with persistent HPT after kidney transplantation (table 1) [12, 14, 17, 18, 22–25].

### *Studies Identified for Sensitivity Analysis*

In sensitivity analyses, we examined the effect of cinacalcet on renal function when including studies meeting less stringent quality criteria. Three studies were identified for the sensitivity analysis on persistent HPT after kidney transplantation [10, 26, 27]. Two studies were excluded from the primary analysis for their high variability in follow-up time among patients (3–18 months) and one for not being peer reviewed.

### *Statistical Analysis*

The primary outcome of the pooled analysis was the mean difference in renal function before cinacalcet initiation and at follow-up of each study. As renal function was assessed by serum creatinine in micromoles per liter or GFR in milliliters per minute, we calculated the pooled random-effects mean difference and 95% confidence interval (CI) between pre- and post-treatment values divided by the pooled standard deviation (Hedges's *g*). The correlation factor pre-/post-treatment serum creatinine was calculated from raw data ( $r = 0.95$ ,  $n = 22$ ) from 2 studies [14, 22] and was used as an estimate for the others. Results from all studies were then pooled using random effects models.

Heterogeneity among studies was explored using the *Q*-statistic as a test (considered significant for  $p < 0.10$ ) and  $I^2$  that ranges between 0 and 100% with lower values representing less heterogeneity. Predefined subgroup analyses were performed for mean difference in serum calcium levels using visual inspection, and random-effect meta-regression analysis.

To assess potential publication bias, we used the Begg's and Egger's tests and Begg's funnel plot; no evidence of bias was seen. Statistical analysis was performed using comprehensive meta-analysis (CMA) version 2.

**Table 1.** Studies that assessed renal function before cinacalcet treatment (BL) and at follow-up (FU) in renal allograft recipients with persistent hyperparathyroidism (HPT)

Study, year	Study design	FU months	Study patients enrolled (n male)	Age, years (range)	BL serum creatinine $\mu\text{mol/l}$	BL GFR ml/min (range)	BL serum calcium mmol/l (range)	BL and final cinacalcet dose, mg/day
<i>Kidney transplantation persistent HPT, included in primary analysis</i>								
El-Amm, 2007 [12]	cohort retrospective	6	18 (8)	45 $\pm$ 13	159 $\pm$ 97	59	2.54 $\pm$ 0.22	30 (60)
Serra, 2007 [14]	cohort prospective	4	12 (6)	59 $\pm$ 2	116 $\pm$ 30	56 $\pm$ 16.6	2.73 $\pm$ 0.14	30 (34)
Serra, 2008 [22]	cohort prospective	1	10 (6)	59 (47–70)	134 $\pm$ 35	49.7 $\pm$ 18.3	2.55 $\pm$ 0.19	30 (60)
Bergua, 2008 [25]	cohort prospective	12	9 (1)	61.8 $\pm$ 5.8	140 $\pm$ 30	51.4 $\pm$ 10.5	2.92 $\pm$ 0.1	30 (45)
Borchhardt, 2008 [24]	cohort prospective	1.5	32 (22)	56 (21–71)	138 $\pm$ 15	48 (17–90)	2.77 (2.71–2.80)	30 (30)
Szwarc, 2006 [17]	cohort prospective	6	9 (9)	52 $\pm$ 11	NA	49.8 $\pm$ 18.6	2.75 $\pm$ 0.15	30 (55)
Kruse, 2005 [18]	cohort retrospective	3	14 (7)	23–65	140 $\pm$ 56	NA	2.72 $\pm$ 0.11	30 (30)
Kamar, 2008 [23]	cohort prospective	12	11 (6)	50.5 (29–65)	119 $\pm$ 48	56 $\pm$ 17	2.68 $\pm$ 0.17	60 (60)
<i>Kidney transplantation persistent HPT, included in sensitivity analysis</i>								
Srinivas, 2006 [16]	cohort retrospective	3–18	11 (6)	48.5 (22–64)	134 $\pm$ 42.1	NA	2.71 $\pm$ 0.1	30 (NA)
Apostolou, 2006 [10]	cohort retrospective	3–18	7 (4)	56 $\pm$ 11	140 $\pm$ 18	NA	1.89 $\pm$ 0.15	30 (NA)
Lopez, 2009 [27]	cohort prospective	13	29 (14)	56 $\pm$ 11	NA	45 $\pm$ 16	2.78 $\pm$ 0.2	30 (60)
Values denote mean $\pm$ SD. NA = Not available.								

## Results

A total of 1,157 articles were found in our initial search, 1,095 of which could be excluded by screening the titles and abstracts (fig. 1). A further 51 articles were excluded because they did not meet the inclusion criteria. Four studies were excluded due to duplicates. Table 1 displays the characteristics of the 8 studies that met our inclusion criteria and of the 3 studies that were included in the sensitivity analysis. All studies were performed to test the efficacy of cinacalcet on PTH and calcium reduction.

### Primary Analyses of Studies on Persistent HPT after Kidney Transplantation

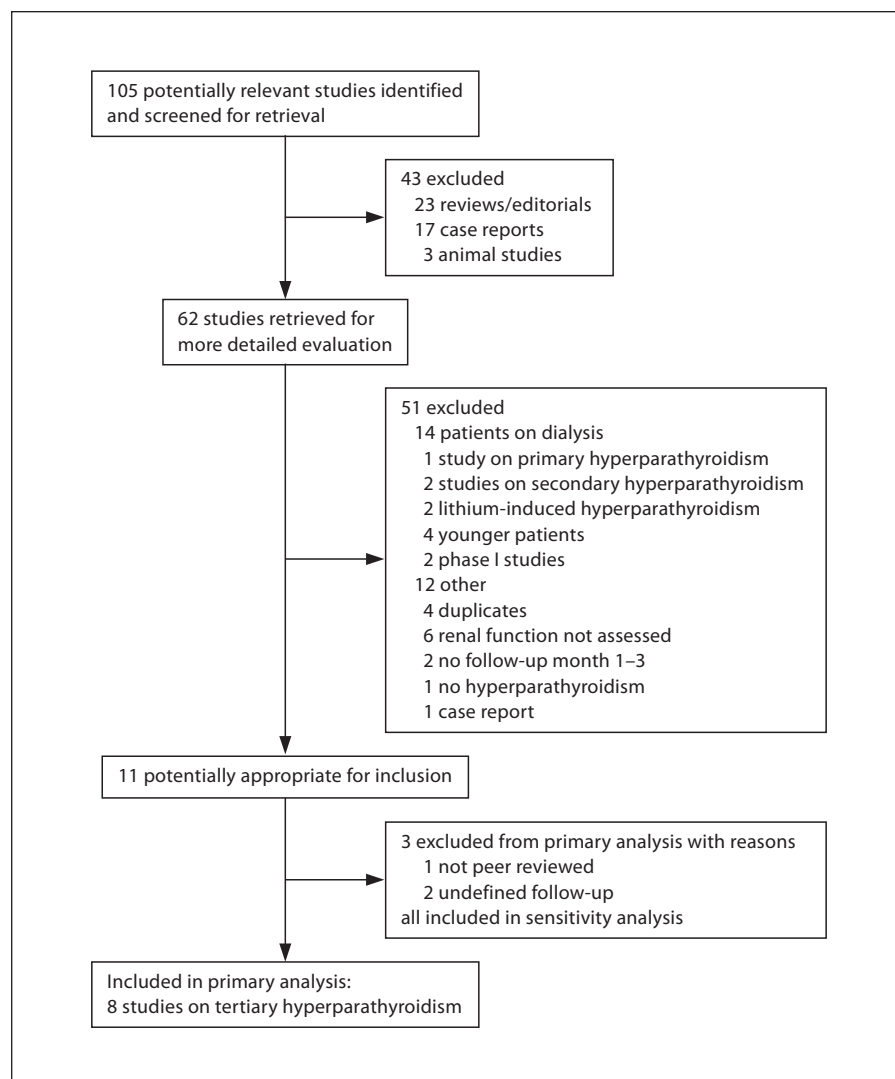
Eight studies involved a total of 115 patients (mean age 53.6 years) with stable allograft function (mean time after transplantation 37.8 months, range 6–74 months) [12, 14, 17, 18, 22–25]. Mean follow-up was 5.7 months (range 1–12 months). Cinacalcet was given at a start dose of 30 mg/day in 7 studies and 60 mg/day in 1 study. At end of follow-up, the mean dose was 47.25 mg/day (table 1).

Figure 2 shows the forest plot for the mean difference in renal function (as Hedges's  $g$ ) under treatment with cinacalcet in renal allograft patients with persistent HPT. Pooling the 8 studies there was a significant association between cinacalcet treatment and the decline of renal function (mean difference of Hedges's  $g$   $-0.188$  (95% CI,  $-0.327$  to  $-0.048$ ),  $p = 0.008$ ). Pooling 7 studies reporting

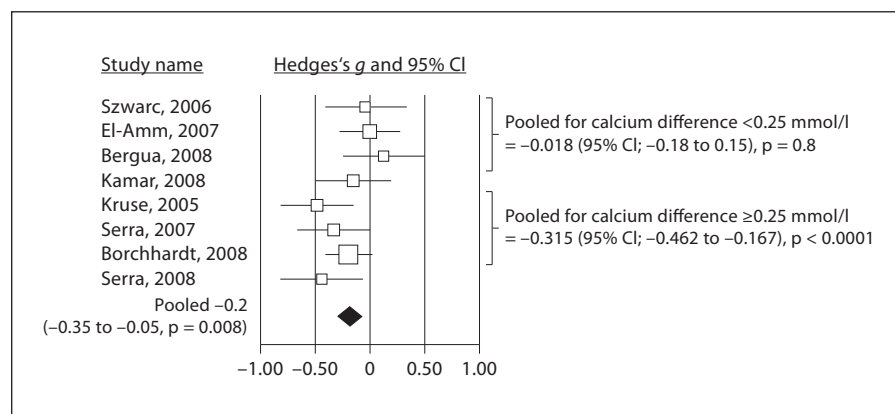
serum creatinine levels, mean serum creatinine increased by  $5 \mu\text{mol/l}$  (95% CI,  $2.4$ – $7.5$ ,  $p < 0.0001$ ). There was no significant heterogeneity in the results among studies (Q-test:  $p$  value =  $0.16$ ,  $I^2$  33.6%) (table 2). In 6 of the 8 studies from our primary analysis concomitant treatment was unchanged. When pooling these studies, the association between cinacalcet treatment and decline of renal function remained significant (mean difference of Hedges's  $g$   $-0.180$  (95% CI,  $-0.310$  to  $-0.051$ ,  $p = 0.006$ ) and no significant heterogeneity in results among studies (Q-test:  $p = 0.34$ ,  $I^2$  11.3%) was detected.

### Subgroup Analysis

Random effects meta-regression analysis revealed a significant association between change in serum calcium levels and decline in renal function (fig. 3;  $\beta = -2.05$ ,  $p = 0.004$ ). For subgroup analysis, studies were dichotomized into studies with higher and lower serum calcium change based on the median. In the low calcium change group [12, 17, 23, 25], the pooled mean difference of Hedges's  $g$  was  $-0.018$  (95% CI,  $-0.186$  to  $0.150$ ) with lower calcium reduction compared to  $-0.315$  (95% CI,  $-0.46$  to  $-0.167$ ,  $p$  value  $< 0.001$ ) for trials with higher calcium reduction [14, 18, 22, 24]. Pooling 3 studies reporting serum creatinine and low delta calcium, serum creatinine remained unchanged ( $0.3 \mu\text{mol/l}$ , 95% CI;  $-9.0$  to  $9.6$ ,  $p = 0.95$ ) and in the high delta calcium group, serum creatinine increased by  $5.6 \mu\text{mol/l}$  (95% CI,  $2.5$ – $8.6$ ,  $p < 0.0001$ ).



**Fig. 1.** QUOROM flow diagram (1,157 articles found, of these 1,052 could be excluded by heading).



**Fig. 2.** Change of renal function during cinacalcet treatment in renal allograft recipients with persistent HPT. Forest plot for Hedges's *g* for change in serum creatinine or creatinine clearance during cinacalcet treatment. Size of squares is proportional to the number of study participants. Error bars represent the 95% CIs.

The confidence limits for the pooled change in renal function are indicated by the diamond-shaped figure. There was no significant heterogeneity (Q-test  $p = 0.16$ ). Among renal allograft recipients with post-transplant persistent HPT, the pooled Hedges's *g* was  $-0.188$  (95% CI,  $-0.327$  to  $-0.048$ ,  $p = 0.008$ ).

**Table 2.** Change of renal function during cinacalcet treatment in renal allograft recipients with persistent hyperparathyroidism (HPT)

Study, year	Change in renal function mean (95% CI)	p value (Q-test), I <sup>2</sup>
<b>Primary analysis</b>		
Szwarc, 2006 [17]	Estimated GFR, ml/min −0.9 (−9.9 to 8.1)	
Kruse, 2005 [18]	Serum creatinine, μmol/l −8.0 (−13.2 to −2.8)	
El-Amm, 2007 [12]	0.0 (−26.9 to 26.9)	
Serra, 2007 [14]	−12.0 (−24.1 to 0.1)	
Bergua, 2008 [25]	4.0 (−7.9 to 15.9)	
Borchhardt, 2008 [24]	−3.0 (−6.3 to 0.3)	
Kamar, 2008 [23]	−8.0 (−25.9 to 9.9)	
Serra, 2008 [22]	−6.0 (−10.9 to −1.1)	
Pooled (random)	−5 (−7.5 to −2.4), <b>p &lt; 0.0001</b>	0.2, 34%
<b>Subgroup analysis</b>		
Mean difference serum calcium pre-/post-cinacalcet <0.27 mmol/l [12, 23, 25]	Serum creatinine, μmol/l 0.3 (−9.0 to 9.6), p = 0.95	0.6, 0%
≥0.27 mmol/l [14, 18, 22, 24]	−5.6 (−8.6 to −2.5), p < 0.0001	0.5, 0%
<b>Sensitivity analysis</b>		
All persistent HPT [10, 12, 14, 16–18, 22–25]	Hedges's g −0.100 (−0.193 to −0.007), p = 0.035	0.055, 46%
Pooled (random) for studies reporting serum creatinine included in the primary analysis, subgroup analysis and sensitivity analysis.		

### Sensitivity Analysis

After adding 3 studies that did not meet our criteria for the primary analysis (table 1) to the 8 trials of the primary analysis (total n = 162 individuals), the pooled mean difference of Hedges's g was −0.100 (95% CI, −0.193 to −0.007, p = 0.035). However, variation among the 11 trials was larger than expected (Q-test: p = 0.043, I<sup>2</sup> 47%), suggesting that the follow-up time point introduces heterogeneity.

### Discussion

Based on small observational studies, we found an association between cinacalcet treatment and a decline in renal function among renal allograft recipients with persistent HPT. The decline of renal function was related to the degree of calcium reduction during a follow-up of 1–3 months.

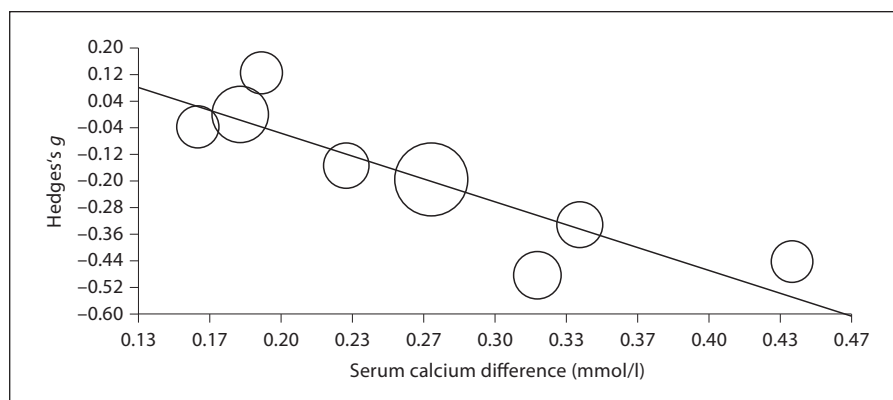
We found a small but significant (p = 0.008) decline in renal function observed in our meta-analysis. In 5 of 8 studies eligible for primary analysis, renal function tended to decline. After adding 3 studies (total n = 162 pa-

tients) that did not meet our criteria for primary analysis, the pooled mean difference remained significant. Pooling 7 studies reporting serum creatinine levels, the mean serum creatinine increased by 5 μmol/l. The difference was highly significant (p < 0.0001) although the absolute difference appears to be small. The serum creatinine high intersubject variability may have diminished the true difference in our study and thus we cannot exclude that our meta-analysis underestimated the effect. Indeed, we prospectively measured serum creatinine and estimated GFR values in 10 kidney allograft recipients with persistent HPT after cinacalcet treatment initiation, withdrawal and re-exposure. Mean serum creatinine values increased by 12 μmol/l (95% CI 40 to −16) and 11 μmol/l (95% CI 40 to −16) and estimated GFR (MDRD) decreased by 6 ml/min (95% CI −20 to 8) and 6 ml/min (95% CI −21 to 8) after cinacalcet initiation at week 0 and cinacalcet re-exposure at week 30, respectively (fig. 4).

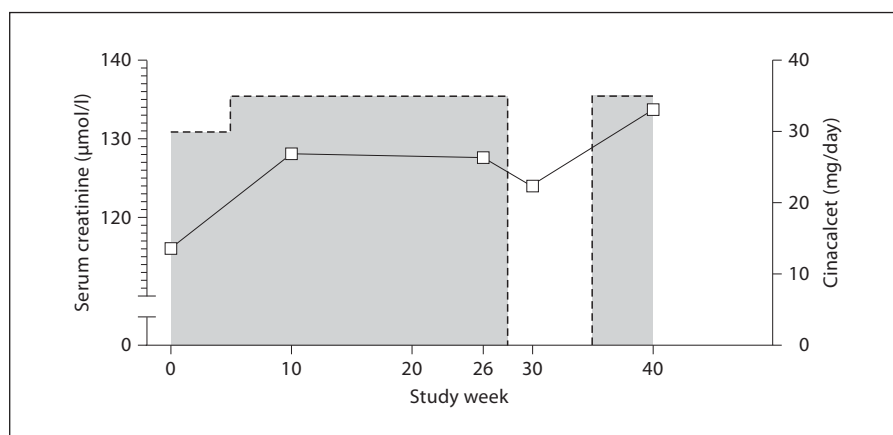
Our observation that cinacalcet initiation, withdrawal and re-exposure quickly changed serum creatinine and was reversible as well as the finding of two studies reporting a restoration of renal function after cessation of cina-



**Fig. 3.** Association between change in serum calcium levels and decline in renal function in patients with persistent HPT 3 months after initiation of cinacalcet treatment. Random effects meta-regression for change in serum creatinine or creatinine clearance (Hedges's  $g$ ) on delta serum calcium during cinacalcet treatment ( $\beta = -2.05$ ,  $p = 0.004$ ). Size of circles is proportional to the number of study participants.



**Fig. 4.** Mean serum creatinine values in 10 kidney allograft recipients with persistent HPT after cinacalcet treatment start, withdrawal and cinacalcet re-exposure. Mean serum creatinine values increased by 12  $\mu\text{mol/l}$  (95% CI 40 to -16) and 11  $\mu\text{mol/l}$  (95% CI 40 to -16) and estimated GFR (MDRD) decreased by 6 ml/min (95% CI -20 to 8) and 6 ml/min (95% CI -21 to 8) after cinacalcet initiation at week 0 and cinacalcet re-exposure at week 30, respectively.



calcet [14, 19], suggest hemodynamic rather than structural effects. The decline in renal function observed in our meta-analysis correlated very well with the delta serum calcium but not with delta PTH. This differential finding can be explained by unchanged pre-dose PTH levels but constantly reduced serum calcium levels over 24 h in cinacalcet-treated kidney transplant patients. Cinacalcet has the unique ability to suppress serum calcium persistently over 24 h, whereas PTH levels are only transiently reduced with a nadir 2–6 h after dosing [22]. Zoledronic acid is a bisphosphonate that lowers serum calcium levels to the same magnitude compared to cinacalcet. In line with our meta-regression results, impairment of creatinine clearance was seen more often in subjects developing hypocalcemia than in those remaining normocalcemic [28], suggesting a common pathophysiological mechanism.

The results of our study have to be interpreted in the context of the available data and its quality, in particular the limited information on changes of concomitant therapy and the absence of an untreated control. However, pooling 6 prospective studies reporting unchanged con-

comitant treatment, cinacalcet treatment was associated with a decrease of renal function. In total, only 8 studies met the inclusion criteria and they were small observational single-center studies in which renal function was not a predefined primary outcome measurement. It is debatable whether the results of such observational studies should be pooled. However, drug safety calls for formal meta-analyses as adverse effects are rare and unlikely to be found in studies designed for efficacy endpoint. It is also well accepted that the quality of a meta-analysis depends largely on the quality of the rough data. The remarkably low heterogeneity in our study indicates robustness of the meta-analysis and gives support to our hypothesis of a decline in renal function in relation to the decrease of serum calcium which is in line with two previous reports of renal function restoration after cinacalcet withdrawal [14, 19]. Information on the measured GFR was not available. However, a change in renal allograft function within an interval of 3 months can reliably be assessed by serial measurements of serum creatinine levels in stable long-term kidney transplant patients.

In summary, our results suggest that cinacalcet has a small but significant effect on renal function for a short-time after cinacalcet initiation in kidney transplant patients with persistent HPT. Our meta-analysis underscores the need for frequent monitoring of creatinine and calcium levels during cinacalcet treatment.

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## Disclosure Statement

The authors declare that they have no competing interests.

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